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Cloning, expression and site-directed mutagenesis of the rat liver 3-alpha-hydroxysteroid dehydrogenase

by *Pawlowski, John E.*, Ph.D., University of Pennsylvania, 1993, 182 pages; AAT 9413888

Advisor:	Penning, Trevor M.
School:	University of Pennsylvania
School Location:	United States -- Pennsylvania
Index terms(keywords):	hydroxysteroid dehydrogenase, steroid
Source:	DAI-B 54/12, p. 6147, Jun 1994
Source type:	DISSERTATION
Subjects:	Pharmacology
Publication Number:	AAT 9413888
Document URL:	http://proquest.umi.com/pqdweb?did=746028701&sid=1&Fmt=2&cli entId=19649&RQT=309&VName=PQD
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Abstract (Document Summary)

Hydroxysteroid dehydrogenases (HSDs) are essential enzymes for the biosynthesis and degradation of steroid hormones. Metabolites of the 3α-HSD pathway are implicated in the development of prostatic hypertrophy and 3α-hydroxy-metabolites of progesterone in the CNS have sedative hypnotic properties due to their interaction with the GABA receptor. The highest levels of 3α-HSD expression are seen in rat liver and this enzyme has been well characterized. Rat liver 3α-HSD has been purified in this laboratory and in addition to catalyzing the oxidoreduction of glucocorticoids, androgens and progestins, it also catalyzes the oxidation of trans-dihydrodiols of polycyclic aromatic hydrocarbons to reactive ortho-quinones and thereby may represent a pathway of carcinogen activation. Hepatic 3α-HSD is also involved in bile acid metabolism and can be potently inhibited by nonsteroidal anti-inflammatory drugs.

The ability of 3α-HSD to recognize these diverse substrates made elucidation of its structure a primary goal of the laboratory. The structural determination of 3α-HSD involved affinity-labeling, x-ray crystallography, and the molecular biological approaches of cloning and site-directed mutagenesis. Prior to the beginning of this project, no HSDs had been cloned and little was known about the structural relationships between 3α-HSD and other HSDs. Obtaining the sequence for rat liver 3α-HSD demonstrated that it was not structurally similar with other HSDs including human placental 17β-HSD and rat liver 11β-HSD, except that it did contain a conserved Tyr-X-X-X-Lys pentapeptide seen in other HSDs. This tyrosine was subsequently found to be essential for catalysis in 11β-HSD. The greatest degree of sequence identity was seen between 3 α-HSD and aldose reductase and other members of the aldo-keto reductase family. The x-ray crystal structure of human placental aldose reductase has recently been determined, and using it as a search model in conjunction with the deduced amino acid from the cDNA, the x-ray crystal structure of rat liver 3α-HSD has been solved. The crystal structures of aldose reductase and 3α-HSD suggested that Tyr-55 could act as the general acid of catalysis. Mutagenesis of Tyr-55 to Phe-55 abolished enzyme activity. In contrast, mutating the tyrosine residue which was conserved with the other HSDs had no effect on catalysis by 3α-HSD. In conjunction with the x-ray crystallographic data, site-directed mutagenesis suggests that Tyr-55 may be the general acid of catalysis in 3α-HSD.

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L1            4 S (E3 OR E6 OR E7) AND (GLUCOCORTICOID (W) RECEPTOR)
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L2            3 S (E3 OR E100 OR E101 OR E102 OR E103 OR E104 OR E105) AND (GLU
                E MONTANA V G/AU 25
L3            3 S (E4 OR E5 OR E6 OR E7) AND (GLUCOCORTICOID (W) RECEPTOR)
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L4            3 S (E3 OR E78 OR E79 OR E80) AND (GLUCOCORTICOID (W) RECEPTOR)
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L5            2 S (E3 OR E4) AND (GLUCOCORTICOID (W) RECEPTOR)
L6            5 S L1 OR L2 OR L3 OR L4 OR L5

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L8        30305 S GLUCOCORTICOID (W) RECEPTOR
L9          210 S L8 AND (CRYSTAL OR (ATOMIC (W) STRUCTURE) OR (ATOMIC (W) COO
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L11           3 S L10 AND FLUTICASONE

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S2	2797	glucocorticoid adj receptor	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/09/01 07:48
S4	70	S2 and (fluticasone adj propionate)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/09/01 07:49
S5	45	S4 and crystal	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/09/01 08:36
S6	2797	glucocorticoid adj receptor	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/09/01 08:34
S7	2	S6 near2 crystal	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/09/01 08:34
S8	18	S6 and crystal.clm.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/09/01 08:37
S9	358	S6 and ((atomic adj coordinates) or (three adj dimensional) or (structural adj coordinates))	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/09/01 08:38
S10	24	S6 and ((atomic adj coordinates) or (three adj dimensional) or (structural adj coordinates)).clm.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/09/01 08:39
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S12	0	glucocorticoid and tif2 and fluticasone	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/09/12 14:07
S13	65	glucocorticoid and tif2	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/09/12 14:21

S14	14	glucocorticoid and tif2 and crystal	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/09/12 14:29
S15	1072	fluticasone adj propionate	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/09/12 14:29
S16	70	S15 and (glucocorticoid adj receptor)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/09/12 14:31
S17	3	S16 and rational	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/09/12 14:30
S18	45	S16 and crystal	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/09/13 09:34
S19	2541	nuclear adj receptor	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/09/14 11:13
S20	198	S19 and (tif2 or (translation adj initiation adj factor))	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/09/14 11:17
S21	1	S20 and fluticasone	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/09/14 11:17
S22	2813	glucocorticoid adj receptor	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/09/14 11:17
S23	114	S22 and (tif2 or (translation adj initiation adj factor))	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/09/14 11:17
S24	1	S23 and fluticasone	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/09/14 11:29
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S26	47899	bledsoe.in. or lambert.in. or montana.in. or stewart.in. or xu. in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/09/15 10:31
S27	25	S26 and (glucocorticoid adj receptor)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/09/15 10:31
S28	18	S27 and crystal	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/09/15 10:32
S29	24	S27 and (crystal or structur$)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/09/15 10:32